Draft for Comment:

Consensus Guidelines for the Design of Clinical Trials in Spatially Fractionated Radiation Therapy for Head and Neck Cancer

Introduction

Spatially fractionated radiation therapy (SFRT), the treatment of tumors with intentionally non-uniform dose, is a complex radiotherapy concept of increasing interest in clinical and experimental radiation oncology. Pilot studies show high tumor response and low toxicity with SFRT in patients treated with palliative or curative intent for bulky tumors (1-6) including head and neck (H&N) cancer (1-3). However, no prospective randomized or multi-institutional clinical trials of SFRT have been conducted. Consensus on complex SFRT clinical trial design parameters is essential to enable broad participation and successful accrual in future SFRT trials, while facilitating trial designs that incorporate relevant physics metrics as well as enable translational studies of SFRT. Such consensus is challenged by the highly variable SFRT technologies and techniques, the complex dosing concepts, and the overall still limited clinical experience with SFRT in the definitive treatment of specific primary malignancies. The purpose of this guideline was to develop a common approach for future multi-institutional clinical trial design in SFRT specific to H&N cancer.

Following an initial literature review, the consensus was developed by a group of recognized SFRT experts who rated a comprehensive set of clinical trial design categories (detailed in the guideline). Anonymized voting results were shared among an Expert Panel and discussed, followed a second voting round, re-discussion of the anonymized results, a repeat literature review and development of the draft recommendations presented here.

This document represents draft consensus recommendations that are posted for review and comment. These draft recommendations are not intended to be reproduced, disseminated or used as a clinical treatment guideline. For details on the consensus process, see link on Radiosurgery Society website, www.therss.org.

SFRT Clinical Trial Design Consensus Guideline for H&N Cancer

These clinical trial design recommendations are guided by three SFRT outcome studies of multiple disease sites containing head and neck (H&N) cancer patients (1-3), three disease-specific studies of H&N cancer patient cohorts (4-6), review of the overall SFRT literature as well as the clinician, physicist and biologist experience on the multidisciplinary Expert Panel for SFRT clinical trials in H&N cancer.

Eligible Disease Sites

Based on the patient characteristics of the published outcome studies (4, 5), the Panel

considers oropharynx and hypopharynx tumors appropriate (high consensus) for inclusion into clinical SFRT trials. Nasopharyngeal tumors are appropriate (4, 5) (moderate consensus) and advanced skin primaries with bulky lymph node involvement can be included (high consensus). Uncommon primary sites, such as salivary gland and paranasal sinus tumors, should be excluded because of their different spread pattern, often variable histology and overall low incidence (high consensus). While oro-, hypo-, nasopharynx, supraglottic and glottic larynx primaries are considered eligible, it is recognized that there is currently insufficient clinical evidence in favor of specific individual H&N primary sites for inclusion into SFRT trials (high consensus).

Eligibility/Exclusion criteria: Disease Stage, Tumor Size/Extent/invasion

There was high consensus that eligible tumor stage/size is guided by the lymph node status, *not* the status (T-stage) of the primary site disease site. The Panel emphasizes that the vast majority of reported clinical experience (1-6) clinical practice with SFRT in H&N cancer is in the treatment of bulky lymph nodes (not the primary tumor). Patients with any T-stage *and* N3 lymph node stage, i.e. lymph node size of more than 6 cm, of either individually or matted lymph nodes, are eligible for an SFRT trial.

The Expert Panel strongly and unanimously recommends that tumors with both carotid invasion and skin involvement, or both carotid invasion and prior radiation therapy be excluded from clinical trials. This exclusion is based on the experience of fatal carotid bleeding in a patient with carotid invasion and prior radiation (5) and unpublished experience of fatal carotid bleeding in a patient with both carotid invasion and skin involvement after SFRT.

Eligibility/Exclusion criteria: Histology

Eligible histologies should include squamous cell carcinoma, based on the majority of the published clinical experience. Inclusion of patients with bulky tumors that are HPV (P16) positive should be considered (moderate consensus). Uncommon and highly radiosensitive histologies, such as sarcoma or lymphoma should be excluded (high consensus).

Eligibility/Exclusion criteria: Prior treatment

Recurrent tumors after prior surgery. Recurrent tumors after prior treatment may be included if the recurrence consists in bulky neck recurrence, and if the target region was not previously irradiated.

Recurrent tumors after prior radiation therapy. Consensus was moderate regarding prior radiation therapy. Exclusion of patients with prior radiation therapy was favored by the Panel (moderate consensus) to minimize potential confounding variables for of the outcome analysis. A separate subsequent clinical trial was suggested for patient populations with recurrence after prior radiation, to follow an initial trial with radiotherapy-naïve patients.

Prior chemotherapy. Prior chemotherapy, including neoadjuvant chemotherapy, is not recommended for clinical trial enrollment because of potential of variable responses prior to

the trial regimen that may confound interpretation of the outcome endpoints.

Eligibility/Exclusion criteria: Patient factors (age, toxicity risk factors)

Enrollment of patients at least 18 years of age was agreed with high consensus, and no upper age limit, as long as performance status is acceptable, was favored. Individual patient risk factors for toxicity should be considered. Patients with scleroderma (systemic sclerosis) should be excluded (high consensus).

Stratifications

Recommended stratifications include T-stage, preferably stratified by grouping of stages T1/T2 vs. T3/T4 and HPV status. In this special case of a highly technology-dependent trial, stratification was recommended according to SFRT technology of GRID vs. Lattice therapy (if Lattice were to be used in the future) and individual GRID techniques (high consensus). No other disease or treatment parameters, such as concurrent chemotherapy, which is employed commonly in H&N cancer, were recommended for stratification.

Pre-treatment Evaluations (clinical, imaging, histologic investigations)

Pretreatment evaluation according to standard of care was recommended, including for imaging maxillofacial/neck CT and/or MRI and PET/CT (high consensus); swallowing study and fiber optic laryngoscopy where applicable; pertinent laboratory studies; and chest CT with the inclusion of upper abdomen/liver for metastatic workup. All enrolled patients should have HPV testing of their tumor (high consensus).

Radiation Therapy: SFRT Dose

Based upon outcome data (1-6) the preferred SFRT will schedule is a dose of 15 Gy in one fraction to the gross tumor target of the bulky lymph node(s). In two of the three published H&N cancer cohorts, 15 Gy was the most commonly used dose schedule and was associated with high local tumor control and a low level of toxicity (4, 6), thus providing the basis for this recommendation. While a schedule of 20 Gy in 1 fraction has been used in one of the three disease-specific outcome studies in H&N cancer cohorts (5), and in a small proportion of patients in other studies (3, 4, 6), overall the higher dose of 20 Gy has been employed more commonly in the palliative setting (1-3). Therefore and because no dose response relationship favoring the higher dose is identifiable, the Panel considers 15 Gy in 1 fraction the preferred dosing regimen for an initial trial of definitive SFRT in H&N cancer (high consensus).

It is emphasized that the EUD must be determined for any trial dose regimen, particularly in view of different GRID technologies (collimator based and MLC-based), which have different dose distributions. MLC based GRID therapy may form a lattice-like GRID pattern if more than one gantry angle are used. EUDs can provide comparisons between plans and must be calculated for both tumor and normal tissues. EUD can be computed using the modified linear quadratic model (MLQ), classical equation or empirical approximation equations, as further detailed in the respective SFRT physics guideline publications (7, 8).

Radiation Therapy: SFRT Target volume

The Panel recommends unanimously that the tumor target should consist in the bulky nodal mass, not in the primary tumor because of very scant outcome data of applying SFRT to the primary tumor. Based on the available clinical outcome data (3-6), the target (PTV) should include the GTV, consisting of the gross tumor of the lymph node mass by imaging, without an additional margin (high consensus).

Radiation Therapy: SFRT: Normal Organ-at-Risk structures

Based on published data (3-6)and the Panel's clinical experience, critical normal organ-at-risk (OAR) structures, include spinal cord, brainstem and optic chiasm structures (high consensus). Consideration of brachioplexus, carotid artery and mandible as OARs may be appropriate (moderate consensus). Regarding the carotid artery, ineligibility of patients who have carotid involvement *and* skin involvement and/or carotid involvement *and* have received prior irradiation, should be noted. These structures are excluded from the SFRT volume. The addition of PRV margins to the OAR structures can be considered, particularly to the spinal cord and brainstem (moderate consensus).

Radiation therapy – SFRT: SFRT technique

Both GRID technologies, collimator-based and MLC-based GRID therapy are the preferred SFRT technologies at this time. Collimator-based and MLC-based GRID may be applied within the same trial, under the condition that EUD has been determined and is comparable. While there was overall support for Lattice therapy as an SFRT technology in H&N cancer in the future, to date (at the time of this writing), there is no published data on the use of Lattice therapy in H&N cancer. Therefore the Panel favors GRID therapy technologies for initial clinical trials unless solid clinical outcome experience on Lattice therapy emerges.

Radiation therapy – Conventional ERT: Dose and technique

Conventionally fractionated external beam radiation therapy (ERT) must be given immediately following SFRT, and it has been demonstrated that tumor response is inferior when SFRT is given without the addition of conventional radiation therapy (1, 2).

For the conventional radiotherapy portion of treatment, conventional definitive dose regimens, specific to the H&N disease site are applied as the dose prescription. PTV doses are generally in the range of 70-72 Gy to the primary gross tumor, 60-63 Gy to the high-risk subclinical target, and 50-56 Gy to the low-risk subclinical target (high consensus). In the SFRT literature for H&N cancer, the conventional doses to gross tumor PTV ranged from 66 Gy (combined with SFRT of 20 Gy/1 faction)(5); to 70 Gy (median; range 68-79 Gy) (4) ; and 69.96 to 72.08 Gy in 2.12 Gy/fraction (6); with conventional doses to intermediate and low-risk PTVs (5). Reduction of the definitive conventional radiotherapy dose below these dosing regimens is not recommended. In one study response rate was only 25% if conventional ERT doses were lower than 75% of the planned definitive dose (6).

The use of IMRT is encouraged (high consensus) and the use of a simultaneously integrated

boost (SIB) was considered appropriate for other bulky areas of involvement, while cautioning that an SIB may add additional variability to the treatment regimen.

Radiation therapy – Conventional ERT: OAR constraints

Dose constraints to OARs for the conventional ERT portion of treatment were recommended to follow those in standard practice without consideration of the dose contribution from the SFRT component of treatment (high consensus).

On-therapy Evaluations: Evaluate feasibility

On-treatment evaluations should include regular (customarily weekly) toxicity assessments, quality-of-life assessments and patient reported outcomes, along with routine imaging that typically includes CBCT imaging for response assessment and adaptive therapy as needed.

Specimen collection of blood and urine at multiple times during radiation therapy for translational correlative science studies of SFRT should be strongly considered (high consensus). The collection of such specimens is feasible in a trial, particularly as patients, who commonly have concurrent chemotherapy, already undergo regular blood collections as the clinical standard of care, and this "liquid biopsy" concept can be leveraged for correlative science studies. While pre-therapy tumor biopsies are available for correlative studies, tumor tissue sampling *during* the treatment course was considered not to be clinically practical or generally feasible based on the potential clinical risk. Functional and/or molecular imaging may be considered to assess vascular or metabolic parameters during ongoing therapy within the tumor volume.

Concurrent systemic therapy: Agents and timing

Chemotherapy and targeted systemic therapy agents that are typically considered appropriate in conjunction with standard-fractionation radiation therapy for H&N cancer are acceptable for a clinical trial (high consensus). These agents typically include but may not be limited to platinum-based chemotherapies, Taxanes and Cetuximab. Chemotherapy can be given concurrently during the radiation therapy course for the conventionally fractionated component of radiation therapy. However, systemic therapy should *not* be given *during* the SFRT component of treatment (high consensus). Typical schedules that have been clinically employed consist of the SFRT fraction given first (without systemic therapy), followed by conventional radiation therapy/concurrent systemic therapy start within 72 hours. This can be accomplished, for example by delivering the SFRT fraction on a Friday and starting concurrent radiation/systemic therapy on the following Monday.

Concurrent systemic therapy: Immunotherapy

There is no published experience with the combination SFRT and immunotherapy. There has been no consensus among the voters on combinations of SFRT and immunotherapy, and the Panel favors not include immunotherapy for an initial trial. Combinations with immunotherapy, which are of particular interest in SFRT from a biology standpoint, should be tested in a subsequent trial, and be guided by the ablative stereotactic radiation and immunotherapy

experience.

Post-therapy Evaluations: Clinical, imaging

Overall, post-therapy response and outcome assessments follow generally accepted clinical standards. Clinical evaluation includes pertinent physical examinations that may include fiber-optic exams as indicated for response and toxicity assessments (high consensus). Trial assessments for quality-of-life and patient reported outcomes are recommended (high consensus). Imaging studies maxilla/facial/neck CT and/or MRI and a 3-month post therapy PET/CT was recommended.

Knowledge Gaps that May be Addressed through SFRT Clinical Trials in H&N Cancer

Clinical knowledge gaps identified by consensus voters and Expert Panel include a better understanding of SFRT dose and fractionation; tolerance to SFRT; and appropriate combination therapies and optimal inclusion of chemotherapy/immunotherapy into SFRT regimens. The differences and impact of SFRT on systemic and local control outcomes is not sufficiently understood and is well suited to be addressed by prospective clinical trials.

As current clinical data are primarily based on SFRT for the treatment of bulky lymph nodes, the potential role of SFRT for the treatment of the primary tumor remains an open question, as is the role of SFRT in patients with moderate bulk of disease. Physician education is an unmet need.

Knowledge gaps in the *physics* of SFRT focus on standardization of SFRT delivery systems, and the standardization of SFRT's unique dosimetric metrics (as detailed in recent guidelines (8)) to be applied in clinical trials. The use of *standardized* metrics in clinical trials is critical to allow robust correlations of heterogeneous dose properties with tumor and normal tissue outcomes, to broaden our understanding of heterogeneous dose properties and response, and to develop optimized dose prescription.

Knowledge gaps in area of *biology* include mechanisms of action; immunological effects; the elucidation of biological cues that can be harnessed for improved outcomes; and the exploration of tumor and normal tissue volume effects on response.

Conclusion

SFRT clinical trials in H&N cancer are feasible based on the clinical experience provided by the pilot studies. Recommendations for eligibility aim to establish a uniform patient cohort of advanced oropharynx, larynx and nasopharynx primaries with bulky lymph node involvement,

while excluding uncommon primary sites and histologies to minimize confounding variables that may hamper the interpretation of the outcome results. Patients with squamous cell carcinoma, both HPV-negative and HPV-positive, should be enrolled. The current experience supports SFRT to bulky *lymph nodes* rather than the primary tumor. GRID technology is favored over Lattice radiotherapy based the technologies used in current pilot studies. A single SFRT fraction of 15 Gy is recommended, and is followed by full-dose conventional (uniform) external beam radiation therapy. Reporting of inhomogeneity dose parameters according to recent SFRT physics guidelines, particularly EUD is highly recommended to allow data interpretation, plan comparison and correlation of dose parameters with clinical outcome. Concurrent chemotherapy agents used in standard-of-care are permitted for the conventional (uniform) external beam radiation therapy of treatment, not for the SFRT component. Pre-therapy, on-therapy and post-therapy investigations to assess tumor control and toxicity endpoints generally follow the standard of care, and should include patient reported outcomes. Specimen collection (blood, urine), synchronized prospectively with the treatment course, for translational correlative science studies is highly recommended. However aside from pre-therapy (diagnostic) biopsies and post-therapy tissue in cases of recurrent disease, tumor tissue collection during therapy for correlative science is challenging in the current clinical environment.

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